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THE AGE DISTRIBUTION OF NEUTRALIZING ANTIBODIES AGAINST VARICELLA-ZOSTER VIRUS IN HEALTHY INDIVIDUALS

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SUMMARY A seroepidemiological survey of varicella was made in the Nagoya area by the neutralization (NT) test. Of 1,473 recorded cases of varicella, 81.4% were under 6 years old and 9.6% were under one year old; of the 168 recorded cases under one year old, about 30% were under 5 months old. Examination of 11 pairs of mother and cord sera and 13 pairs of mother and infant sera showed that transfer of NT antibody was in general good, even in babies that were small for their age or small at birth after 28 weeks gestation. The transferred maternal antibody decreased rapidly, becoming undetectable in babies of 4 months old. Then with increase in age the percentage of seropositive children gradually increased, being 53.3% at 4 to 5 years old, and 100% in those of over 9 years old, with a temporary decrease in young adults in their twenties.

INTRODUCTION

Varicella, caused by primary infection with varicella-zoster virus (VZV), is one of the commonest communicable diseases in childhood. Formerly, the complement fixation (CF) test was routinely used for detecting antibody to VZV. However, since after infection CF antibody usually decreases rapidly to an undetectable level, this test has been thought to be unsuitable for examining the immune status of individuals to VZV (Gold and Bodek, 1965). Recently, sensitive and specific assays for detecting antibody to VZV, such as tests of fluorescent antibody to membrane antigen (FAMA) and immune adherence hemagglutination (IAHA) have been developed and applied in serological studies on VZV infection (Gershon et al., 1976; Kalter et al., 1977; Wong et al., 1978; Yamada et al., 1979).

These tests were comparable to the NT test in sensitivity (Yamada et al., 1979). The presence of NT antibodies to VZV should be the most reliable indication of past infection and of presumed immunity to varicella. We previously described a simplified NT test for VZV (Asano and Takahashi, 1978) and used it to examine the immune status to varicella and the antibody response after inoculation of a live varicella vaccine in both normal and immunocompromised individuals (Asano et al., 1977a, b; Asano and Takahashi, 1977; Ozaki et al., 1978). This paper reports a serological survey of varicella in Aichi prefecture made using this simplified NT test.

MATERIALS AND METHODS

1. *Clinical surveillance*

The survey was made in three areas in Aichi prefecture: Fujiyamadai, Handa city and Tokoname city. Clinically diagnosed varicella patients were recorded at Fujiyamadai Clinic, Handa City Hospital and Tokoname City Hospital during a five or six year period until 1976. The ages of all varicella patients were recorded in Handa and Tokoname cities, and those of patients of under one year old were recorded in all three areas.

2. *Blood samples*

The following serum samples were collected from healthy individuals residing in Aichi prefecture: 1, 32 cord blood sera from normal term babies, 11 of which were paired with maternal sera, 2, 111 sera from children ranging in age from newborn infants to 13-year-old children, including 11 babies of low-birth-weight, 3, 59 sera from adults, including 24 maternal sera which were paired with those of their offspring. The history of contraction of varicella were carefully recorded when each sample was obtained, but the histories of adults were obscure or unreliable. All specimens were stored at −20°C until examined.

3. *Neutralization test*

The NT test described previously (Asano and Takahashi, 1978) was used for detection of antibody. The cell-free virus used in the test was prepared by ultrasonic disruption of human embryonic lung (HEL) cells infected with the Oka strain (Takahashi et al., 1975) of VZV. About 75 plaque forming units of the virus were used as antigen. Serum samples diluted two-fold from 1:4 to ≧1:32 were mixed with the antigen and used for infection of HEL cells after incubation at 37°C for one hour. NT antibody titers are expressed as the highest dilutions of the serum causing 50% or more reduction in the plaque count compared with that of the virus control.

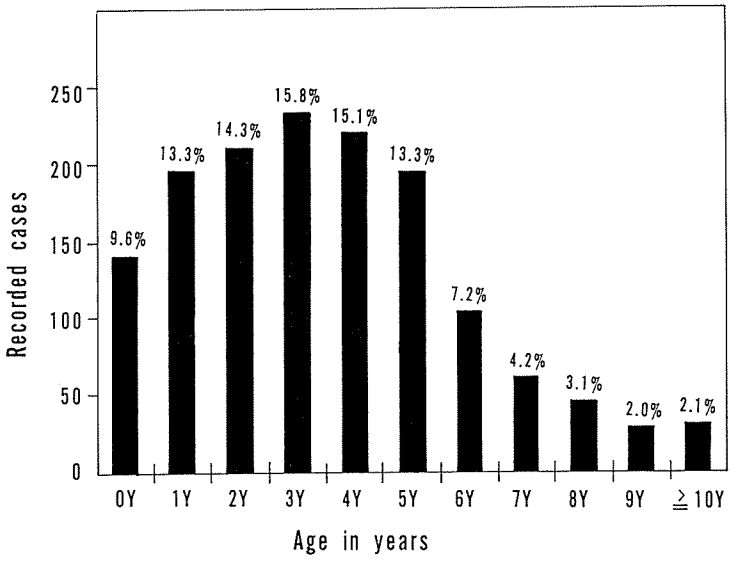


FIGURE 1. Age distribution of 1473 recorded cases of varicella in Handa city hospital (1971–1975) and Tokoname city hospital (1971–1976).

RESULTS

1. *Age distribution of recorded cases of varicella*

The age distribution of recorded cases of varicella is shown in Fig. 1: 1473 cases were recorded in Tokoname (1971–1976) and Handa (1971–1975) city hospitals. The peak was at 3 years of age and most (81.4%) of the cases were under 6 years old; 144 cases

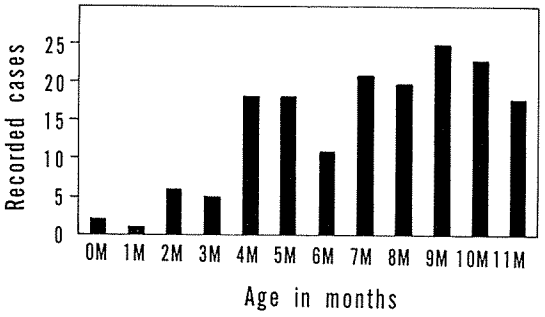


FIGURE 2. Distribution by months of 168 recorded cases of varicella during the first year of life in Handa city hospital, Tokoname city hospital and Fujiyamadai clinic (1971–1976).

(9.6%) were under 1 year of age. After 6 years of age, the number of cases fell rapidly with increase in age. The distribution of 168 recorded cases of under one year of age is shown in Fig. 2. These cases were recorded in Tokoname (1971–1976) and Handa (1971–1975) city hospitals and Fujiyamadai clinic (1971–1976). About 30% of them were in the 0–5 month age group and about 70% in the 6–11 month age group.

2. *Placental transfer of maternal antibody*

The antibody titers in 11 paired sera of mothers and cord blood of infants obtained during normal deliveries showed almost the same NT titers (Fig. 3). Results in the other 13 pairs of mother-infant sera are illustrated in Fig. 4, according to the weight of the babies at birth. Placental transfer of antibody seemed in general to be good in newborn infants, even in babies who were small for their age or small at birth after 28 weeks gestation.

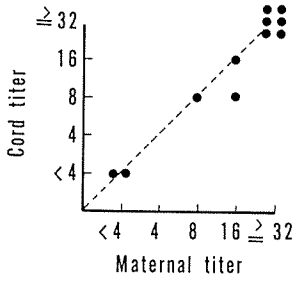
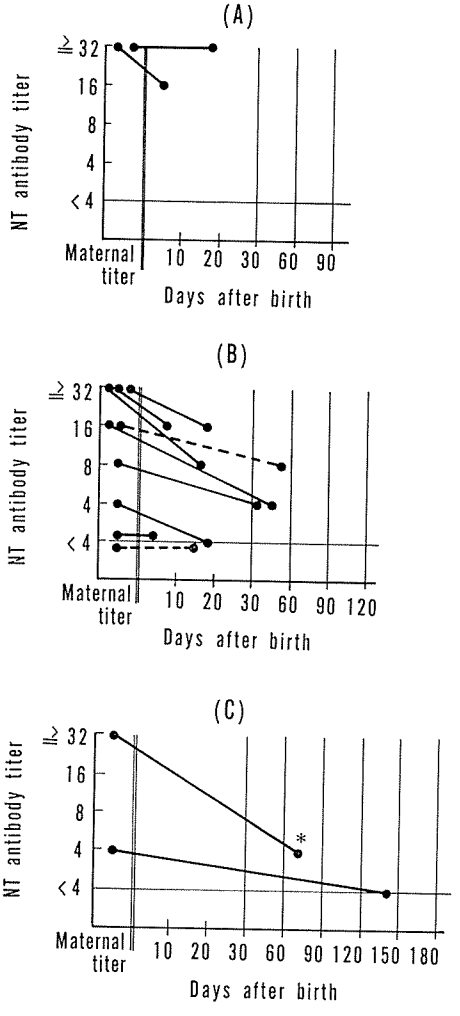


FIGURE 3. NT antibody titers of 11 pairs of full-term cord and maternal sera.



* The baby's gestatinal age was 28 weeks and one day.

FIGURE 4. Relation of baby's birth weight to NT antibody titers of 13 pairs of mother-infant sera.

Birth weight: (A), more than 2,500 g; (B), 1,500 to 2,500 g; (C), less than 1500 g. The baby's birth weight was between the 10th percentile and the 90th percentile for the gestational age using the Portland fetal growth curves (●——●); The birth weight was below the 10th percentile (●------●).

3. *Distribution of NT antibody during the first year of life*

A total of 32 cord blood samples were tested. They were obtained during normal deliveries at full term. Of these, 27 (84.4%) were seropositive. Serum samples were collected from 44 healthy children of under one year of age, 11 of whom were newborn infants who were small at birth. None of the children had any history of varicella. The sera of 17 (38.6%) infants had detectable antibody with titers ranging from 1:4 to ≧1:32. The antibody titers in seropositive infants decreased rapidly after one month of age and antibody was detectable in only 2 children of 5 months old or more, who seemed to have subclinical infection (Fig. 5).

4. *Age distribution of antibodies in children and adults*

The NT antibody titers of a total of 170 serum specimens were measured, and the results are shown in Fig. 6. In children of over one year old, the percentage of seropositive cases gradually increased with age: the percentage of seropositive children was 53.3% at 4 to 5 years old, and 100% at over 9 years of age. The seropositive rate dropped to 71.4% at 20–29 years of age and then 100% inolder adults.

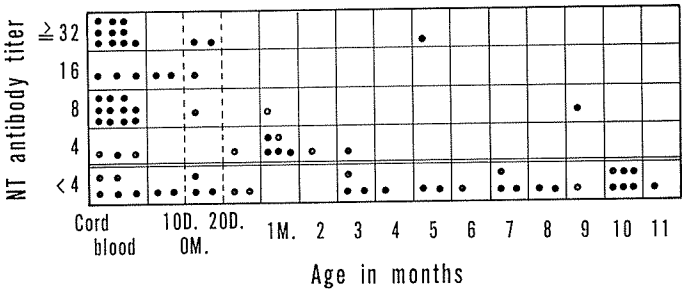


FIGURE 5. NT antibody titers of 76 sera during the first year of life. None of the infants had any history of varicella.

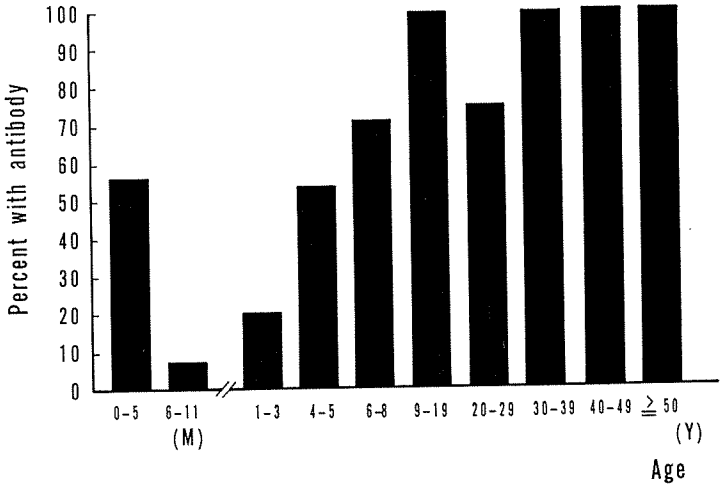


FIGURE 6. Relation of age to positive rate of NT antibody in 111 infants and children, and 59 adults.

DISCUSSION

This report describes a clinical and serological survey of varicella in Aichi prefecture. Weller (1976) made a similar survey in Massachusetts over a 4-year period, finding that varicella is most frequent in children of 5 to 9 years old. We found that the highest incidence was between in children of 1 to 5 years old. This lower age of incidence is probably partly becasue in Aichi prefecture almost all children of 3 to 5 years old examined were attending kindergarten, where they had an increased chance to come in contact with VZV. From our clinical experience, we have the impression that infants during the first year of life contract varicella more frequently than other viral infections such as measles. In this survey we recorded

9.6% of varicella were during the first year of life, and about 30% of 168 recorded cases of varicella of under 1 year old were under 5 months old.

We used the NT test for the serological survey. The NT test is too complex and slow for routine clinical use, but it is the most reliable method for detecting specific antibody and for measuring the immune status to VZV. In this work we used a simplified NT test recently reported by Asano and Takahashi (1978). Our study demonstrated that placental transfer of antibody from the mother to the fetus is generally good, since all the umbilical cord sera examined had almost the same NT antibody titer as that of the mother (Fig. 3). In early infancy the sera showed transplacentally acquired maternal NT activity, even in babies who were small for their age and in babies born after 28 weeks' gestation (Fig. 4). Raker et al. (1978) reported that about 90% of the low-birth-weight infants they examined, even those of less than 1,500 g, had detectable antibody to VZV by the FAMA test.

Gershon et al. (1976) also reported a serological survey of antibody to VZV in infants during the first year of life measured by the FAMA test. They found that maternally transmitted antibody to VZV was rapidly lost within the first year of life, and by 5.5 months of age, 50% of the infants no longer had detectable passively acquired VZ antibody. In our study by the NT test, the titers in seropositive infants seemed to decrease and disappear even more rapidly. This rapid loss of antibody may explain why young babies acquire varicella much more frequently than measles.

After one year of age, the incidence of seropositive children increased with age, and almost all children were found to be infected with VZV clinically or subclinically by 9 years of age. The incidence of antibody was slightly lower (71.4%) in adults in their 20's and again approached 100% in their 30's. Wong et al. (1978) similarly found that the incidence of antibodies to VZV measured by IAHA test increased with age. They found that primary infections usually occurred between the ages of 4 and 12 years, teenage children all had detectable antibodies to VZV, and the positive rate decreased temporarily in adults in their 30's. Antibodies in early life probably result from primary infection with VZV. These antibodies may then gradually decrease with time, and be boosted by subclinical reinfection from the offspring or in response to reactivation of latent virus later in life.

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